Remarks

Courtesies extended to Applicants' representative in the personal interview held May 19, 2004, are acknowledged with appreciation.

The present invention provides transgenic mice whose genome contains a transgene comprising a gene encoding a human steroid and xenobiotic receptor (SXR) polypeptide operably linked to an albumin promoter/enhancer, wherein the SXR polypeptide is a member of the steroid/thyroid hormone superfamily and forms a heterodimer with retinoid X receptor; the resulting heterodimer binds to a defined response element, and activates transcription in response to a wide variety of natural and synthetic steroid hormones. Invention transgenic mice express SXR polypeptide in at least one of the liver and intestine.

In one aspect of the invention, inducible expression of SXR polypeptide (controlled by the albumin promoter/enhancer) activates in the transgenic mouse a response to natural and synthetic steroid hormones to which a wild type mouse does not respond. In another aspect of the invention, constitutive expression of SXR polypeptide (controlled by a combination of the albumin promoter/enhancer and the VP16 activation domain) results in hepatomegaly and growth retardation in the transgenic mouse as compared to a wild type mouse.

In another embodiment, the invention provides transgenic knock-out mice whose genome comprises a disruption in an endogenous SXR polypeptide gene, wherein said disruption prevents production of a functional SXR polypeptide and results in the transgenic knockout mouse exhibiting decreased response to natural and synthetic steroid hormones as compared to a wild-type mouse.

In another embodiment, the invention provides methods for producing transgenic mice by injecting a one-cell mouse zygote with a transgene comprising a gene encoding a human steroid and xenobiotic receptor (SXR) polypeptide operably linked to an inducible or a constitutively active

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promoter/enhancer (e.g., albumin promoter/enhancer or the combination of the albumin promoter/enhancer and the VP16 activation domain), and obtaining from the zygote a transgenic mouse that expresses SXR polypeptide in the liver, thereby activating in the transgenic mouse a response to the natural and synthetic steroid hormones to which a wild type mouse does not respond.

Claims 13-42 were pending before this Response. By the present communication, claims 13, 14, 17, 24, 25, 28, 31, 35, 37-39, 41 and 42 have been amended, and claims 20, 32 and 33 have been canceled. No new matter is introduced by the subject amendments as they are fully supported by the Specification and original claims. Accordingly, claims 13-19, 21-31 and 34-42 are currently pending. A complete listing of all of the pending claims, with an indication of the status thereof, is presented in the Listing of Claims, beginning at page 2 of this communication.

Change of Address

Applicants request that the current mailing address for the above-identified application be duly noted in the PTO records to avoid further mis-mailing of official communications. Applicants have repeatedly requested updating of PTO records, but official communications continue to be mailed to old, outdated addresses. Correction is respectfully requested. For the Examiner's convenience, a copy of a previously submitted "Change of Address" request is included herewith.

Sequence Information

The Examiner's assertion that the claims allegedly include sequences not identified by SEQ ID NOs (see page 1 of the Office Action) is respectfully submitted to be in error. As discussed at the personal interview, the only sequence information presented in the claims makes reference to short nucleotide sequences (6 nucleotides), which are not of sufficient length to require labeling with a sequence identifier.

The Rejection under 35 U.S.C. § 112, First Paragraph—Written Description

The rejection of claims 13-42 under 35 U.S.C. § 112, First Paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is respectfully traversed.

By the present communication, the claims have been amended to make specific reference to the albumin promoter/enhancer, optionally in the further presence of the VP16 activation domain. As discussed at the personal interview, and as acknowledged by the Examiner in the Office Action "[t]he specification provides adequate written description for a transgenic mouse whose genome comprises a transgene operably linked to the albumin promoter/enhancer which encodes a human steroid and xenobiotic receptor (SXR) polypeptide as set forth in SEQ ID NO:2, and a transgene operably linked to the albumin promoter/enhancer which encodes a fusion protein comprising the activation domain of VP16 from herpes simplex virus and the amino terminal of SXR (VPSXR)." (See page 2, lines 17-22 of the Office Action).

With respect to the Examiner's concern as to what is encompassed by the phrase "SXR polypeptide," this terminology is further defined in the claims with reference to both structure (e.g., member of the steroid/thyroid hormone superfamily) and function (e.g., forms heterodimers with a specified partner, binds to defined response elements, and activates transcription in response to a diverse array of compounds). Indeed, this definitional language is fully consistent with the language of recently issued parent application, now issued as United States Patent No. 6,756,491.

Accordingly, in view of the above remarks and the amendments submitted herewith, reconsideration and withdrawal of this rejection are respectfully requested.

The Rejection under 35 U.S.C. § 112, First Paragraph—Enablement

The rejection of claims 13-42 under 35 U.S.C. § 112, First Paragraph, as the specification allegedly fails to enable any person skilled in the art to which it pertains, or with which it is most

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nearly connected, to practice the invention commensurate in scope with these claims, is respectfully traversed.

As noted above, by the present communication, the claims have been amended to make specific reference to the albumin promoter/enhancer, optionally in the further presence of the VP16 activation domain. As discussed at the personal interview, and as acknowledged by the Examiner in the Office Action, the specification is enabling for "a transgenic mouse whose genome comprises a transgene operably linked to the albumin promoter/enhancer, wherein said transgene comprises a polynucleotide sequence which encodes a human steroid and xenobiotic receptor (SXR) polypeptide. . ." (See page 5, lines 10-13 of the Office Action). As further discussed at the personal interview, and as further acknowledged by the Examiner in the Office Action, the specification is also enabling for "a transgenic mouse whose genome comprises a transgene, wherein said transgene comprises; a) a transgene which encodes a fusion protein comprising the VP16 activation domain of the herpes simplex virus and the amino terminal of SXR. . ." (See page 6, lines 2-5 of the Office Action).

Specifically with respect to claim 23, Applicants respectfully disagree with the Examiner's assertion that "there is no indication that another SXR family member exists." (See page 10, line 11 of the Office Action). Contrary to the Examiner's assertion, there is substantial disclosure throughout Applicant's specification confirming that other SXR family members exist. See, for example, page 10, lines 28-29, which make reference to PXR, the rodent homolog of SXR. See also page 39, lines 2-15 where comparison between the human and mouse homologs is presented. In addition, page 42, lines 12-26 make reference to an additional member of the SXR family of receptors. Still further indications of the existence of additional SXR family members are found throughout Applicant's specification, see, for example, page 16, lines 18-19; page 42, lines 2-9; page 49, lines 12-18; and page 50, lines 5-20.

Applicants further disagree with the Examiner's assertion that "it is not clear that such knock-out mice could be created..." (see page 10, line 13 of the Office Action). Contrary to the

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Examiner's assertion, having possession of the information provided by the present specification, preparation of a variety of genetically modified mice would be a straightforward exercise for one of skill in the art. See, for example, Genes and Development 14:3014-3023 (2000; copy provided herewith for the Examiner's convenience), which describes the preparation of numerous transgenic mice; Nature 406:435-439 (2000; copy provided herewith for the Examiner's convenience), which explicitly describes generation of PXR-null mice (see page 438, column 2); and Proc Natl Acad Sci USA 98:3375-3380 (2001; copy provided herewith for the Examiner's convenience), which describes additional investigations with both transgenic mice and PXR-null mice. Thus, contrary to the Examiner's assertion, preparation and manipulation of knock-out mice as contemplated by the present claims are well within the skill of the artisan, in view of the extensive disclosure of the present application.

Accordingly, in view of the above remarks and the amendments submitted herewith, reconsideration and withdrawal of this rejection are respectfully requested.

The Rejection under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 13-42 under 35 U.S.C. § 112, Second Paragraph, as allegedly being indefinite, is respectfully traversed.

Specifically with respect to claims 13-16, 21, 24-17, 35 and 39-42, Applicants respectfully disagree with the Examiner's assertion that it is allegedly not clear what is encompassed by a SXR polypeptide (see the last three lines at page 11 of the Office Action). As noted, this terminology is further defined in the claims with reference to both structure and function. See also, recently issued parent application, U.S. Patent No. 6,756,491. The terminology employed herein is fully consistent with the terminology used to define SXR polypeptides in the recently issued parent.

Specifically with respect to the Examiner's assertion that claim 13 is allegedly unclear (see page 12, lines 13-18 of the Office Action), the subject language is respectfully submitted to

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be clear, and is fully consistent with the terminology used to define SXR polypeptides in the recently issued parent application.

The Examiner's further assertion with respect to the clarity of claim 13 (at page 12, line 19 - page 13, line 3 of the Office Action) has been obviated by the amendments submitted herewith. Thus, claim 13, as amended, now makes specific reference to the albumin promoter/enhancer.

With respect to the Examiner's assertion that claims 14, 23 and 36, are allegedly vague and unclear based on the recitation of "a response" (See page 13, lines 4-7 of the Office Action), each of the subject claims are respectfully submitted to be clear in requiring a different response by invention transgenic animals upon exposure to specific compounds (i.e., steroids and xenobiotics) then the response displayed by wild-type animals when exposed to the same compounds. The metes and bounds of a different response as between two distinctly different animals is respectfully submitted to be clear. Moreover, with specific reference to claim 14, this rejection has been rendered moot by the amendments submitted herewith.

The Examiner's assertion that the recitation of "the ligand binding domain and DNA binding domain" in claim 16 allegedly lacks antecedent basis in claim 13 is submitted to be in error. Claim 13 specifically identifies SXR as a member of the steroid/thyroid hormone superfamily. Such receptors are known in the art to have several well characterized domains, including a ligand binding domain and a DNA binding domain. Thus, claim 16 is fully supported by claim 13.

The Examiner's assertion that claim 23 is allegedly unclear is respectfully submitted to be in error. What could be more clear than a "decreased response"? Whatever response is displayed by a wild-type mouse upon exposure to steroids or xenobiotics would be reduced in a transgenic mouse according to the invention. Any level of reduction would meet this

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requirement. Clearly, complete loss of response as a result of the disruption to SXR contemplated herein would still meet this claim requirement.

Applicants respectfully disagree with the further assertion by the Examiner that claim 23 is allegedly unclear in the recitation of "an endogenous SXR polypeptide gene." As noted above, there is substantial disclosure throughout Applicant's specification confirming that other SXR family members exist. Any such family member is embraced by the above-referenced claim language. What is endogenous to one host animal would depend on the specific host in question.

The Examiner's concern with respect to the language of claim 24, has been rendered moot by the amendments submitted herewith.

Similarly, the Examiner's concern with respect to the language of claim 25 has been rendered moot by the amendments submitted herewith.

The Examiner's assertion that claims 26 and 27 are allegedly unclear is in error. Since SXR is a member of the steroid/thyroid hormone superfamily of receptors, which are known to have a modular structure, numerous constructs can be prepared using only specific domains derived from SXR. For example, claim 26 contemplates only the ligand binding domain be obtained from SXR, whereas the DNA binding domain could be obtained from any transcription activating factor. In contrast, claim 27 is more specific in requiring that both the ligand binding domain and DNA binding domain be obtained from SXR.

The Examiner's assertion that claim 28 is allegedly vague and unclear has been rendered moot by the amendments submitted herewith, wherein the language of concern to the Examiner has been amended consistent with the discussion thereof at the personal interview.

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Similarly, the Examiner's assertion that claim 31 is allegedly vague and unclear has also been rendered moot by the amendments submitted herewith, wherein the language of concern to the Examiner has been amended consistent with the discussion thereof at the personal interview.

The Examiner's assertion that claim 35 is allegedly incomplete is respectfully submitted to be in error. Contrary to the Examiner's assertion that the final step allegedly results only in a zygote (See page 15, lines 3-4 of the Office Action), the final step of the claim specifically contemplates "obtaining from the zygote a transgenic mouse. . ." Nothing more is required.

In view of the above amendments and remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. 112, Second Paragraph, are respectfully requested.

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Conclusion

In view of the above amendments and remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosure: Copy of previously submitted Change of Correspondence Address
Genes and Development 14:3014-3023 (2000)
Nature 406:435-439 (2000)
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